REMARKS

I. Preliminary remarks

The present application was filed with a preliminary amendment amending claims 6, 7, 10 and 17 and canceling claims 11-13. In response to the restriction requirement mailed October 11, 2006, Applicants elected claims 1-5 and 14 for continued examination. Claims 6-10 and 16-17 were withdrawn by the Examiner from consideration.

It appears that claim 15 was not grouped by the Examiner in the restriction requirement mailed October 11, 2006. In the Office Action mailed July 16, 2007, claim 15 was indicated as being withdrawn. Clarification of the status of claim 15 is respectfully requested.

Claims 1-5 and 15 are amended, new claims 18-25 are added and claims 6-10, 14, 16 and 17 are canceled herein. Claims 6-10, 16 and 17 are canceled as being drawn to a non-elected invention. Applicants reserve the right to pursue such claims in divisional applications.

Support for "purified VEGF-C and purified VEGF-D" recited in amended claim 1 can be found, for example, at paragraph [0050]. Support for "purified plasmin" and "purified serine protease" recited in new claim 18 and 19, respectively, can be found, for example at paragraph [0060]. Support for new claims 20-23 and 25 can be found in original claims 2-5. Support for local administration of the composition recited in new claim 24 can be found at paragraph [0035]. Support for the disorders recited in amended claim 15 can be found, for example, at paragraphs [0036]-[0038]. Claims 2-5 are amended to adopt a preferred article "the" for dependent claims, but not to change the scope or meaning of the claims. Accordingly, no new matter has been added by the amendment to claims 1-5 and 15 and new claims 18-25.

Applicants reserve the right to pursue the subject matter of any claim, whether canceled or in original form, in continuing applications.

II. New Attorney/Agent

A Power of Attorney and change of correspondence address are submitted herewith, and correspondence should now be addressed to Attorney David A. Gass at the address listed below.

III. Amendments to the specification and submission of corrected figures

The Examiner objected to page 4 of the specification because a portion of the page is illegible. In response, Applicants submitted herewith as Appendix A is a replacement page 4 of the specification as filed that is free of copy of marks. The substantive content of page 4 is unchanged in the replacement sheet.

The Examiner further objected to the title of the invention. In response, Applicants have amended to title to reflect the subject matter of the present claims.

Finally, the Examiner requested the submission of corrected Figures that comply with 37 C.F.R. § 1 .84(u)(1) and an amendment to the specification to comply with the drawing requirement. In response, Applicants hereby submit correct Figures along with an amendment to the specification to refer to the corrected Figures. In addition, paragraph [0066] has been amended because this paragraph inadvertently refers to Figure 1 instead of Figure 4. This amendment to the specification is obvious after review of Figures 1 and 4 and the description in paragraphs [0065] and [0066]. In particular, paragraph [0066] refers to a Western blot depicting that plasmin proteolytically processed the VEGF homology domain (VHD) from full-length VEGF-D and from both of the partially processed forms of VEGF-D and specifically refers to plasmin lanes 10^{-5} to 10^{-7} and thrombin lanes 10^{-4} to 10^{-7}. None of Figures 1A-1E depict a Western blot. Figure 4 depicts the Western blot (and in particular the lanes) referred to in paragraph [0066]. Accordingly, no new matter has been added by the amendment to paragraph [0066].

In view of the foregoing, Applicants request that the objections to the drawings and specification be withdrawn.

IV. The rejection under 35 U.S.C. § 102(b) in view of Eibl should be withdrawn.

The Examiner rejected claim 14 under 35 U.S.C. § 102(b) as assertedly being anticipated by Eibl (U.S. Patent No. 5,520,912). The rejection is moot in view of the cancellation of claim 14. Accordingly, the rejection should be withdrawn.

It would be improper to reject amended claim 15 as being anticipated by Eibl because Eibl does not disclose or suggest a method of treatment of a disorder selected from the group consisting of coronary artery disease, lymphedema, restenosis and stenosis comprising administration of a composition comprising an effective amount of a serine protease and a pharmaceutically acceptable excipient.

V. The rejection under 35 U.S.C. § 102(b) in view of Stacker should be withdrawn.

The Examiner rejected claims 1-4 under 35 U.S.C. § 102(b) as assertedly being anticipated by Stacker (J. Biol. Chem., 274:32127-32136, 1999). Applicants request reconsideration of the rejection in view of the amendments made herein and the following remarks.

Amended claim 1 recites "purified VEGF-C and purified VEGF-D." While Stacker discloses that VEGF-D expressed in 293EBNA cells is proteolytically processed and therefore active, it fails to disclose or suggest that treating purified VEGF-D with a serine protease will induce such proteolytic processing. Stacker certainly does not identify a class of proteases (or a specific protease) that induces the proteolytic processed forms of VEGF-D.

New claim 19 recites "a purified serine protease." Stacker fails to disclose or suggest that treating VEGF-D with a purified serine protease will induce proteolytic processing of VEGF-D. Stacker certainly does not identify a class of proteases (or a specific protease) that induces the proteolytic processed forms of VEGF-D.

The first identification of a class of proteases capable of inducing proteolytic processing of VEGF-C and/or VEGF-D is in the present application. Accordingly, Stacker does not anticipate any of claims 1-4 and the rejection should be withdrawn.

It would be improper to reject amended claim 15 as being anticipated by Stacker because Stacker does not disclose or suggest a method of treatment of a disorder selected from the group consisting of coronary artery disease, lymphedema, restenosis and stenosis comprising administration of a composition comprising an effective amount of a serine protease and a pharmaceutically acceptable excipient.

VI. The rejection under 35 U.S.C. § 102(b) in view of Enholm should be withdrawn.

The Examiner rejected claims 1-3 and 5 under 35 U.S.C. § 102(b) as assertedly being anticipated by Enholm (TMC, 8:292-297, 1998). Applicants request reconsideration of the rejection in view of the amendments made herein and the following remarks.

As discussed above in Section IV, amended claim 1 recites "purified VEGF-C and purified VEGF-D." While Enholm discloses that VEGF-C expressed *in vitro* is proteolytically cleaved by proteases to release the active soluble form of the protein, it fails to disclose or suggest that treating purified VEGF-C with a serine protease will induce such proteolytic processing. Stacker certainly

does not identify a class of proteases (or a specific protease) that induces the proteolytic processed forms of VEGF-C.

New claim 19 recites "a purified serine protease." Enholm fails to disclose or suggest that treating VEGF-C with a purified serine protease will induce proteolytic processing of VEGF-C. Enholm certainly does not identify a specific protease (or a class of proteases) that induces the proteolytic processed forms of VEGF-C.

The first identification of a class of proteases capable of inducing proteolytic processing of VEGF-C and/or VEGF-D is in the present application. Accordingly, Enholm does not anticipate any of claims 1-3 and 5 and the rejection should be withdrawn.

It would be improper to reject amended claim 15 as being anticipated by Enholm because Enholm does not disclose or suggest a method of treatment of a disorder selected from the group consisting of coronary artery disease, lymphedema, restenosis and stenosis comprising administration of a composition comprising an effective amount of a serine protease and a pharmaceutically acceptable excipient.

VII. Conclusion

It is believed that the foregoing amendments and remarks respond to all of the objections and rejections found in the Office Action. If the Examiner believes that a telephone conversation would expedite allowance of the claims, she is invited to contact the undersigned agent or David A. Gass, Attorney for Applicants, at the number indicated below. The Director is hereby authorized to charge any fees required with the filing of this paper to Deposit Account No. 13-2855, under Order No. 28967/5794C.

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Respectfully submitted,

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APPENDIX A

[0014] VEGFR-1 and VEGFR-2 bind VEGF with high affinity, and VEGFR-1 also binds VEGF-B and placenta growth factor (PlGF). VEGF-C has been shown to be the ligand for Flt-4 (VEGFR-3), and also activates VEGFR-2 (Joukov *et al.*, *EMBO J.*, 15: 290-298, 1996). A ligand for Tek/Tie-2 has been described (International Patent Application No. PCT/US95/12935 (WO 96/11269) by Regeneron Pharmaceuticals, Inc.); however, the ligand for Tie has not yet been identified.

[0015] The receptor Flt-4 is expressed in venous and lymphatic endothelia in the fetus, and predominantly in lymphatic endothelia in the adult (Kaipainen *et al.*, *Cancer Res.*, 1994 54: 6571-6577; *Proc. Natl. Acad. Sci. USA*, 92: 3566-3570, 1995).

[0016] Vascular endothelial growth factor-D (VEGF-D) is a secreted glycoprotein that binds and activates VEGF receptor-2 (VEGFR-2) and VEGFR-3 (Achen *et al.*, *Proc. Natl. Acad. Sci. USA* 95: 548-553, 1998), cell surface receptor tyrosine kinases expressed predominantly on blood vascular and lymphatic endothelia respectively (for review see Stacker *et al.*, *FASEB J.* 16: 922-934, 2002). VEGFR-3 signals for lymphangiogenesis (growth of lymphatic vessels) (Veikkola *et al.*, *EMBO J.* 20: 1223-1231, 2001) whereas VEGFR-2 is thought to signal for angiogenesis (growth of blood vessels). As would be expected given the receptor specificity of human VEGF-D, this growth factor stimulates both angiogenesis and lymphangiogenesis (Byzova *et al.*, *Blood* 99: 4434-4442, 2002; Veikkola *et al.*, *EMBO J.* 20: 1223-1231, 2001; Marconcini *et al.*, *Proc. Natl. Acad. Sci. USA* 96: 9671-9676, 1999).

[0017] Importantly, VEGF-D stimulated tumor angiogenesis that enhanced solid tumor growth and induced lymphangiogenesis that promoted metastatic spread of tumor cells to the lymphatics and lymph nodes (Stacker *et al.*, *Nature Med.* 7: 186-191, 2001). Recently, VEGF-D expression was reported to be an independent prognostic factor for both overall and disease-free survival in colorectal cancer (White *et al.*, *Cancer Res.* 62: 1669-1675, 2002).

[0018] VEGF-D is secreted from the cell in a relatively inactive form containing an N-terminal propeptide, a C-terminal propeptide, and a central VEGF homology domain ("VHD") containing the binding sites for VEGFR-2 and VEGFR-3 (Achen, M. G., M. Jeltsch, E. Kukk, T. Mäkinen, A. Vitali, A. F. Wilks, K. Alitalo, and S. A.Stacker. 1998. Vascular endothelial growth factor D (VEGF-D) is a ligand for the tyrosine kinases VEGF receptor 2 (Flk-1) and VEGF receptor 3 (Flt-4). Proc. Natl. Acad. Sci. USA95:548-553, Joukov, V., T.